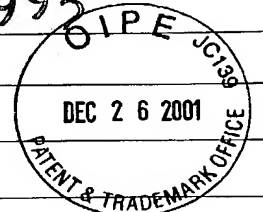


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FORM PTO-1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER D01/200
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U. S. APPLICATION NO. (if known, see 37 CFR 1.5) 107018992
INTERNATIONAL APPLICATION NO. PCT/IL00/00364	INTERNATIONAL FILING DATE June 21, 2000	PRIORITY DATE CLAIMED June 22, 1999
TITLE OF INVENTION STABLE BENZIMIDAZOLE FORMULATION		
APPLICANT(S) FOR DO/EO/US RAFFAEL LAHAV and VALERIE AZOULAY		

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to being national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☒ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☒ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

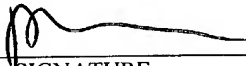
Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A **FIRST** preliminary amendment.
☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☒ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information: .

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U. S. APPLICATION NO. <u>10/018992</u> (If known, see 37 CFR 1.53) INTERNATIONAL APPLICATION NO. <u>PCT/IL00/00364</u>		ATTORNEY'S DOCKET NUMBER D01/200																						
<p>17. <input type="checkbox"/> The following fees are submitted:</p> <p>BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) – (5): Neither international preliminary examination fee (37 CFR 1.482) Nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO And International Search Report not prepared by the EPO or JPO\$970.00</p> <p>International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO\$840.00</p> <p>International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO\$690.00</p> <p>International preliminary examination fee (37 CFR 1.482) paid to USPTO But all claims did not satisfy provisions of PCT Article 33(1) – (4).....\$670.00</p> <p>International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1) – (4).....\$96.00</p> <p>ENTER APPROPRIATE BASIC FEE AMOUNT = \$ 840.00</p> <p>Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30 Months from the earliest claimed priority date (37 CFR 1.492(e)). \$ 130.00</p> <table border="1"><thead><tr><th>CLAIMS</th><th>NUMBER FILED</th><th>NUMBER EXTRA</th><th>RATE</th></tr></thead><tbody><tr><td>Total claims</td><td>49 -20 =</td><td>29</td><td>X \$18.00</td></tr><tr><td>Independent claims</td><td>3 -3 =</td><td>0</td><td>X \$78.00</td></tr></tbody></table> <p>MULTIPLE DEPENDENT CLAIM(S) (if applicable) + \$260.00 \$</p> <p>TOTAL OF ABOVE CALCULATIONS = \$ 1492.00</p> <p>Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28). \$</p> <p>SUBTOTAL = \$ 1492.00</p> <p>Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 Months from the earliest claimed priority date (37 CFR 1.492(f)). \$</p> <p>TOTAL NATIONAL FEE = \$ 1492.00</p> <p>Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be Accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +</p> <p>TOTAL FEES ENCLOSED = \$ 1492.00</p> <table border="1"><thead><tr><th></th><th>Amount to be refunded:</th><th></th></tr></thead><tbody><tr><td></td><td>\$</td><td></td></tr><tr><td></td><td>Charged:</td><td>\$</td></tr></tbody></table>		CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	Total claims	49 -20 =	29	X \$18.00	Independent claims	3 -3 =	0	X \$78.00		Amount to be refunded:			\$			Charged:	\$	<p>CALCULATIONS PTO USE ONLY</p>	
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<p>a. <input checked="" type="checkbox"/> A check in the amount of \$ <u>1492.00</u> to cover the above fees is enclosed.</p> <p>b. <input type="checkbox"/> Please charge my Deposit Account No. _____ in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.</p> <p>c. <input type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. _____. A duplicate copy of this sheet is enclosed.</p> <p>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b) must be filed and granted to restore the application to pending status.</p> <p>SEND ALL CORRESPONDENCE TO:</p> <p>DR. D. GRAESER LTD. C/O THE POLKINGHORNS 9003 FLORIN WAY UPPER MARLBORO MARYLAND 20772 USA</p> <p> SIGNATURE</p> <p><u>D'VORAH GRAESER</u> NAME</p> <p><u>40,000</u> REGISTRATION NUMBER</p>																								

STABLE BENZIMIDAZOLE FORMULATION

FIELD AND BACKGROUND OF THE INVENTION

5 The present invention relates to a novel stable formulation for an acid labile benzimidazole, and methods of preparation and administration thereof, and in particular, for a stable formulation of a benzimidazole which is suitable for oral administration.

 Omeprazole, Pantoprazole, Lansoprazole and other derivatives of benzimidazole, which are active proton pump inhibitors and used conventionally for decreasing gastric secretion are
10 known to be susceptible to degradation and transformation in acid media. Omeprazole, 5-methoxy-2(((4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole, is disclosed and described in European Patent No. 5129 and European Patent No. 124495, as well as in numerous other patents and published patent applications.

 The susceptibility of these active proton pump inhibitor substances to degradation and
15 transformation in acid media increases the difficulty of preparing a pharmaceutical form designed for oral administration. If the active substance comes into contact with the stomach content, which is a highly acidic medium, these chemical substances become degraded. Thus, these benzimidazole derivatives should be protected both during storage and during their passage through the acidic environment of the stomach.

20 The stability of Omeprazole has been extensively studied (see for example A. Pilbrant and C. Cederberg, *Scan. J. Gastroenterol.*, 20: 113-120, 1985). Omeprazole degrades with a half-life of less than 10 minutes in an environment with pH values below 4.0. At pH 6.5, the half life of Omeprazole is 18 hours and at pH 11 about 300 days. Therefore, the environment of Omeprazole should be kept at a sufficiently high pH value in order to maintain the stability of
25 the compound, in a formulation which is suitable as a product for oral administration, for example by locating Omeprazole within a core which also contains alkaline constituents. This leads to an alkaline reaction aimed at improving stability of the active substance during manufacture thereof and during storage of the pharmaceutical formulation.

 In addition, such a formulation must protect Omeprazole from the acidic environment of
30 the stomach, since if Omeprazole is given orally without any protective coating, it will degrade in the acid environment of the stomach. European Patent No. 237,200 discloses one solution, which is to directly coat the solid core containing Omeprazole, or another benzimidazole derivative, with an enteric coating layer.

However, this apparent solution to the instability of Omeprazole caused further complications, in that the alkaline core containing Omeprazole was found to react with the enteric coating, thereby causing the enteric coating to degrade. A solution to these further complications is disclosed in United Kingdom Patent Application No. 2,189,698, in which

5 Omeprazole is contained within a solid active core, which is coated first with a subcoating layer and then with an enteric coating layer. The enteric coating layer protects the Omeprazole during the passage through the stomach, while the subcoating layer protects the enteric coating layer from reacting negatively with the alkaline core containing Omeprazole.

The background art describes other attempts to provide formulations which are suitable

10 for oral administration of acid-labile substances. For example, PCT Application No. WO 97/12581 discloses a composition adapted for oral administration containing Omeprazole which specifically does not include alkaline-reacting compounds. Instead, the composition features a core composed of a nuclei and Omeprazole compressed together, an intermediate layer and an enteric layer.

15 European Patent Application No. 519,144 discloses a formulation for Omeprazole, which features a neutral (sugar) core. Omeprazole is sprayed onto the sugar core, after which an intermediate coating layer and an enteric coating layer are sprayed onto the core.

PCT Application No. WO 98/00114 discloses a modification to other background art formulations for Omeprazole, in which the intermediate subcoating layer is partially neutralized

20 with an alkaline compound. However, this modified formulation still features the subcoating layer, which is a disadvantage in that it complicates the manufacturing process and increases the expense and difficulty of manufacture. Thus, the formulation disclosed in PCT Application No. WO 98/00114, like those disclosed in European Patent Application No. 519,144 and other background art references, has the disadvantage of requiring the intermediate layer.

25 PCT Application No. WO 83/00435 discloses a solid dosage form, such as a capsule or tablet, containing a pharmacologically active agent coated with an anionic polymer, which is insoluble in gastric juice and in intestinal juice below pH 7. The preferred anionic polymer is a partly methyl esterified methacrylic acid polymer in which the ratio of free carboxylic groups to ester groups is about 1:2. In contrast to the present invention, Omeprazole is not disclosed as one

30 of the active agents.

French Application No. 2,692,146 discloses stable compositions of microgranules of gastro-protected Omeprazole. The composition features a center of Omeprazole diluted in mannitol. This center is coated with an intermediate layer featuring mannitol. An enteric

coating is then added over this intermediate layer. PCT Application No. WO 97/12581 discloses a formulation in which an intermediate layer between the core and an enteric coating contains silicium dioxide.

PCT Application No. WO 96/37195 discloses a formulation which lacks a subcoating layer, but which features a core containing titanium dioxide. Both the core containing Omeprazole and the enteric coating layer placed on top of the core include titanium dioxide as an ingredient. Unfortunately, titanium dioxide is only able to mask the discoloration caused by the reaction between Omeprazole and the enteric coating layer, but cannot prevent such an undesirable reaction. Thus, the disclosed formulation does not prevent the undesirable reaction between the benzimidazole derivative and the enteric coating, which is known in the art.

German Patent Application No. 196 26 045 A1 discloses a method for stabilising Omeprazole by coating small tablets or pellets, containing large amounts of mannitol, with a subcoating of Eudragit L. The subcoating of Eudragit L is neutralized, after which a final enteric coat of non-neutralized Eudragit L is applied.

A formulation of a benzimidazole derivative, such as Omeprazole, which lacks an intermediate coating layer and yet which is stable both during storage and during the passage through the stomach, would be highly desirable. Such a formulation would be simpler to manufacture and would expose the sensitive benzimidazole derivative to fewer production steps, thereby decreasing the possibility that the active compound would degrade during production. Unfortunately, such a stable benzimidazole formulation, which lacks an intermediate layer, is not currently available.

There is thus a unmet need for, and it would be useful to have, a stable benzimidazole formulation, particularly for Omeprazole which lacks an intermediate layer and yet which is stable both during storage and during the passage through the stomach.

SUMMARY OF THE INVENTION

The formulation of the present invention contains a benzimidazole derivative, such as Omeprazole, and is able to maintain the stability of this active ingredient without a separating layer. Instead, the enteric coating layer is applied as a solution with a pH value of at least 6.5, and more preferably in a range of from about 7 to about 10, directly to the benzimidazole derivative substrate. This solution, with the optional addition of a plasticizer, can be directly coated onto the substrate without any necessity for an intermediate layer. Furthermore, in this

pH range, the enteric coating is optionally applicable in an aqueous solution, thereby obviating the need for organic solvents for dissolving the enteric coating material.

The resultant formulation maintains the stability of the benzimidazole derivative during storage and at the same time protects the product during passage through the acidic environment of the stomach, where the acidic environment of the stomach causes a partial ionic exchange to occur within the material of the coating. This partial ionic exchange renders the coating impermeable to the acidic liquids of the stomach. On the other hand, during storage the problem of interaction between the enteric coat and the alkaline core is thus completely eliminated as the "enteric coat" is no longer acidic during the storage period.

Preferably, the benzimidazole derivative is selected from the group consisting of Omeprazole, Pantoprazole, Lansoprazole, Leminoprazole, Perprazole, Rabeprazole, and pharmaceutically acceptable salts thereof, as well as any other derivatives of benzimidazole which are proton pump inhibitors and which are conventionally used to decrease gastric secretion.

According to the present invention, there is provided a stable composition for a benzimidazole derivative, the composition comprising: (a) a substrate, the substrate featuring the benzimidazole derivative; and (b) an enteric coating material layered over the substrate, the enteric coating material having a pH value of at least about 6.5.

The substrate can optionally have several different structures. For example, the substrate is optionally an active core containing the benzimidazole derivative, in which the core is a pellet, bead or tablet for example. The active core can be prepared by any conventional method known in the art, including but not limited to, pellets prepared by spheronisation, pellets prepared by coating an inert non pareil seed with Omeprazole, tablets prepared by granulation and compression, as well as any other methods.

The enteric coating material optionally and preferably includes an enteric material selected from the group consisting of hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, polymethacrylic acid methyl methacrylate and polymethacrylic acid ethyl methacrylate.

More preferably, the enteric coating material further comprises an alkaline compound, such that the pH value is adjusted by adding the alkaline compound to the enteric material. Most preferably, the alkaline compound is an inorganic or organic alkaline salt compound. Even more preferably, the alkaline compound is selected from the group consisting of basic sodium,

potassium or ammonium hydroxide. Also most preferably, the pH value is in a range of from about 7 to about 10.

The enteric coating material of the composition could optionally include a plasticizer. Preferably, the plasticizer is selected from the group consisting of a citric acid ester and a phthalic acid ester.

According to another embodiment of the present invention, there is provided a stable composition for a benzimidazole derivative, the composition consisting essentially of: (a) a substrate, the substrate featuring the benzimidazole derivative; and (b) an enteric coating material layered over the substrate, the enteric coating material having a pH value of at least about 6.5.

According to still another embodiment of the present invention, there is provided a method for producing a stable composition for a benzimidazole derivative, the method comprising the steps of: (a) forming a substrate with the benzimidazole derivative; (b) preparing an enteric coating material having a pH value of at least about 6.5; and (c) layering the enteric coating material over the substrate.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The formulation of the present invention contains a benzimidazole derivative, such as Omeprazole, and is able to maintain the stability of this active ingredient without a separating layer between the active compound and an enteric coating layer. Instead, the enteric coating layer is applied as a solution with a pH value of at least 6.5, and more preferably in a range of from about 7 to about 10, directly to the benzimidazole derivative substrate. This solution, with the addition of a plasticizer, can be directly coated onto the substrate without any necessity for an intermediate layer. Furthermore, in this pH range, the enteric coating is optionally applicable in an aqueous solution, thereby obviating the need for organic solvents for dissolving the enteric coating material.

The resultant formulation maintains the stability of the benzimidazole derivative during storage and at the same time protects the product during passage through the acidic environment of the stomach. The problem of interaction between the enteric coat and the alkaline core is thus completely eliminated as the enteric coat at this stage is no longer acidic.

Without wishing to be limited to a single mechanism, it is hypothesized that as the formulation passes through an acidic environment, such as the acidic environment of the stomach, the outer layer of the enteric coat is converted to an acidic form. This acidic form of

the enteric coating material is insoluble in the acidic environment of the stomach. If the formulation is then placed in an environment with a more alkaline pH value, for example by moving into the small intestine, the enteric coat dissolves and releases the active substance.

The use of an enteric coating which includes HPMCP (hydroxypropylmethylcellulose phthalate) neutralized with a basic salt is disclosed in U.S. Patent No. 5,225,202 and in two
5 scientific articles, "Enteric Film Coating Using Completely Aqueous Dissolved Hydroxypropyl Methyl Cellulose Phthalate Spray Solutions" (J.W. Stafford *et al.*, *Drug Development and Industrial Pharmacy*, 8:513-530, 1982) and "The In Vitro and In Vivo Performance of Aqueous Based Enteric Coats of Neutralized Hydroxypropyl Methyl Cellulose Phthalate" (J.R. Bloor *et al.*,
10 *Drug Development and Industrial Pharmacy*, 15:2227-2243, 1989). However, the disclosed enteric coating is not taught or suggested in any of these references as a suitable direct enteric coating for substrates which contain Omeprazole. As noted previously, Omeprazole and the related benzimidazole derivatives are unusually sensitive molecules, and as such must be carefully protected. Furthermore, U.S. Patent No. 5,225,202 teaches the necessity for a subcoat
15 between the drug-containing substrate and the enteric coating for drugs which are not compatible with the enteric coating. By contrast, the present invention has been shown to be highly effective without such a subcoat, which is particularly surprising since the background art teaches that formulations containing Omeprazole or another benzimidazole derivative must also feature a subcoat. Neither scientific article even considers the problems associated with
20 acid-sensitive drugs, and as such cannot teach or suggest the formulation of the present invention.

As shown by both the *in vitro* and *in vivo* data given below, the formulation of the present invention has been shown to be particularly effective for the oral administration of Omeprazole as the exemplary benzimidazole derivative, a result which could not have been predicted from
25 these references. Indeed, the article by J.R. Bloor *et al.* teaches away from the use of such a neutralized enteric coating for any formulation, as this article disclosed good *in vitro* performance of the formulation but poor *in vivo* performance. By contrast, as described in greater detail below with regard to Example 7, the formulation of the present invention shows good performance *in vivo*. Thus, the background art neither teaches nor suggests the direct
30 coating of a substrate containing Omeprazole or another benzimidazole derivative with an enteric coating material having a pH value of at least about 6.5, and in fact teaches away from such a formulation.

The preparation of the benzimidazole-containing compositions of the present invention is described first with reference to the following general description and then with reference to the following non-limiting examples of the preparation and application of the compositions of the present invention.

5 As noted previously, the formulation of the present invention includes a substrate which features the benzimidazole derivative. A solution is prepared with the enteric coating material, which has a pH value of at least 6.5 and more preferably of from about 7 to about 10. Preferably, a pH value in the desired range is obtained by adding an alkaline compound to an enteric coating material. More preferably, the alkaline compound is selected from the group
10 consisting of sodium, potassium or ammonium hydroxide. This enteric coating solution is then layered directly over the substrate to form the composition of the present invention.

The term "substrate" refers to substantially any structure which features the benzimidazole derivative, such as Omeprazole. For example, this structure could be an active core containing the benzimidazole derivative. This active core could be prepared in a number of
15 different ways which are known in the art. For example, the active core could be formed by compressing the benzimidazole derivative with an alkaline substance. As another example, the active core could be prepared by mixing the benzimidazole derivative with an alkaline substance, spheronizing the mixture and then forming cores through pelletisation. As yet another example, the active core is optionally and preferably prepared by embedding the active ingredient in a
20 poloxamer and compressing the embedded material into tablets. The active core is also optionally formed by granulating the active ingredient with an alkaline substance and compressing the granulation into tablets.

Alternatively and optionally, the structure could include a neutral core, such as a sugar bead which does not contain the benzimidazole derivative, over which the benzimidazole
25 derivative is coated. The coating includes Omeprazole or other benzimidazole derivative with a suitable adhesive polymer.

Substantially any type of neutralized suitable enteric coating material could be used in order to coat the benzimidazole substrate, including but not limited to, cellulose acetate phthalate (CAP); hydroxypropyl methylcellulose phthalate (HPMCP); polyvinyl acetate phthalate;
30 cellulose acetate trimellitate; polymethacrylic acid methyl methacrylate or ethyl methacrylate, such as the various types of Eudragit; and hydroxypropyl methylcellulose acetate succinate (HPMCAS). However, preferably the enteric coating material is prepared with the proviso that this material does not contain HPMCP alone, but only in combination with at least one of these

7 other listed enteric coating materials. The particularly preferred enteric coating material is HPMCAS.

As used herein, the term "neutralized enteric coating material" refers to enteric coating material which has been at least partially neutralized by reaction with an alkaline compound, which is preferably a basic inorganic salt. Preferably, the enteric coating material is at least
5 about 60 % neutralized, more preferably the enteric coating material is at least about 80 % neutralized, and most preferably the enteric coating material is at least about 95 % neutralized.

The enteric coating optionally contains a plasticizer, such as a citric acid ester, a phthalic acid ester, or any suitable plasticizer.

10 The method for applying the enteric coating material to the substrate can vary. Substantially any coating method can be used, such as pan coating or fluidized bed coating, with the solution of the enteric coat chosen. As noted previously, preferably this solution is an aqueous solution. The enteric coating materials described previously can be applied to the substrate in an aqueous solution if the pH value of the solution is adjusted to at least 6.5, and
15 more preferably to an alkaline value, most preferably a pH value from about 7 to about 10.

The following specific examples illustrate various aspects of the compositions of the present invention, and are not intended to be limiting in any way. Specific reference is made to Omeprazole for the purposes of description only and without intending to be limiting.

20 Example 1

This example of the composition of the present invention was prepared as follows. The substrate was in the form of an active core, which was prepared by embedding Omeprazole in poloxamer (Pluronic PE 6800), granulating the resulting mass, adding the necessary auxiliary
25 substances to the mass, and compressing the resultant material into tablets. The substrate was then coated with alkaline polyvinyl acetate phthalate as the enteric coating layer.

Substrate (Active Embedded Core)

<u>Ingredients</u>	<u>Quantity per tablet</u>
Omeprazole	20 mg
Poloxamer (Pluronic PE 6800)	200 mg
Colloidal silicon dioxide	7 mg
Magnesium carbonate	10 mg
Sodium starch glycolate	12 mg
Titanium dioxide	100 mg
Ludipress ®	226 mg
Sodium stearyl fumarate	25 mg

Enteric coating layer

Polyvinyl acetate phthalate	75 mg
Antifoam emulsion	0.25 mg
Sodium hydroxide	12 mg

- 5 For the preparation of the substrate, the poloxamer was melted at a temperature of 80 °C. Omeprazole, together with 2 mg colloidal silicon dioxide, 8 mg of magnesium carbonate, titanium dioxide and 6 mg of sodium starch glycolate were added and mixed thoroughly. Mixing was continued until the melt solidified. The melt was granulated and the rest of the ingredients added to the granulate. The granulate was then compressed into tablets which
- 10 contained 20 mg Omeprazole. These tablets, which formed the substrate of the composition, were then transferred into a conventional coating pan and coated with the enteric coating layer, prepared in the following manner. First, the antifoam emulsion was dissolved in water to form an aqueous solution. Polyvinyl acetate phthalate was then stirred into this solution for a final concentration of about 10% weight per volume before sodium hydroxide was added. Sodium
- 15 hydroxide (1 M solution) was then added to adjust the pH value of the solution to about 8, thereby obtaining a basic solution of the enteric coating material. This solution was then sprayed onto the tablets with an incoming air temperature of 40 °C.

Example 2

- 20 This example of the composition of the present invention was prepared as follows. The substrate was prepared by embedding Omeprazole in poloxamer (Pluronic PE 6800) to form

tablets, as for Example 1. However, in this Example, the tablets were then coated with hydroxypropyl methylcellulose acetate succinate (HPMCAS) as the enteric coating layer.

Substrate

<u>Ingredients</u>	<u>Quantity per tablet</u>
Omeprazole	20 mg
Poloxamer (Pluronic PE 6800)	200 mg
Colloidal silicon dioxide	7 mg
Sodium starch glycolate	20 mg
Ludipress ®	228 mg
Sodium stearyl fumarate	25 mg

5 Enteric coating layer

Hydroxypropyl Methylcellulose Acetate Succinate (HPMCAS)	43 mg
Triethyl citrate	12 mg
Sodium lauryl sulfate	1.3 mg
Talc	21.4 mg
Sodium hydroxide	2.3 mg

The tablets were prepared as for Example 1, except that titanium dioxide was omitted. The tablets were then coated in a conventional coating pan with the enteric coating solution, which was prepared as follows. First, triethyl citrate was dissolved in water to form an aqueous solution. Sodium lauryl sulfate was then added to this aqueous solution. The HPMCAS and talc
 10 were dispersed in this solution, such that the concentration of HPMCAS was about 10% weight per volume. Sodium hydroxide (1M solution) was then added to adjust the pH value of the solution to a value from about 7 to about 10. The enteric coating was layered over the substrate by spraying the solution with an incoming air temperature of 40 °C.

15

Example 3

This example of the composition of the present invention was prepared as for Example 1, except that the enteric coating contained alkaline HPMCP (hydroxypropylmethylcellulose phthalate) rather than HPMCAS.

Substrate

<u>Ingredients</u>	<u>Quantity per tablet</u>
Omeprazole	20 mg
Poloxamer (Pluronic PE 6800)	200 mg
Colloidal silicon dioxide	7 mg
Sodium starch glycolate	10 mg
Titanium dioxide	83 mg
Ludipress ®	145 mg
Sodium stearyl fumarate	25 mg

Enteric coating layer

HPMC Phthalate (HP-55)	56.2 mg
Triethyl citrate	22.5 mg
Sodium hydroxide	9 mg

5

The substrate was prepared as described in Example 1, and was then coated in a conventional coating pan with the enteric coating solution by spraying the solution at an incoming air temperature of 40 °C. The enteric coating solution was prepared as follows. The HPMC phthalate was suspended in the water to a concentration of about 10% weight per volume (before sodium hydroxide was added). Sodium hydroxide (1M solution) was then added to this aqueous suspension until the HPMCP dissolved. The resultant solution has a pH value in a range of from about 8 to about 10. The triethyl citrate was then added to the resultant solution in order to form the enteric coating solution, which was then layered over the substrate as previously described.

15

Example 4

In this example of the composition of the present invention, the substrate has two parts: a neutral core; and a coating layer containing the active ingredient, which was layered over the neutral core. The substrate was then coated with the enteric coating solution. Hard gelatin capsules were then filled with the resultant pellets.

20

Substrate**Neutral core****Quantity per capsule**

Sugar spheres 20/25 (700-850 microns)	161.63 mg
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Active coating

<u>Ingredients</u>	<u>Quantity per capsule</u>
Omeprazole	20.00 mg
Hydroxypropyl methylcellulose 2910	5.33 mg
Hydroxypropyl cellulose	6.00 mg
Lactose	8.00 mg
Disodium phosphate anhydrous	0.64 mg
Sodium lauryl sulfate	0.50 mg

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Enteric coating layer

HPMCAS	21.00 mg
Triethyl citrate	6.00 mg
Sodium lauryl sulfate	0.66 mg
Talc	11.00 mg
Sodium hydroxide	1.12 mg

10

The composition of the present invention was prepared according to this Example as follows. First, sugar spheres were placed in a fluid bed coating chamber, equipped with a Wurster bottom spraying device. A suspension of the ingredients in water was then prepared so that the concentration was approximately 20 % of total solids in water. This active coating suspension was sprayed onto the sugar spheres. A suspension of the enteric coating was prepared according to Example 2. This enteric coating was then sprayed onto the substrate in order to form the finished pellets. The pellets were then placed in capsules.

15

Example 5

20

This example of the composition of the present invention was prepared with a compressed tablet as the substrate. The tablet was then coated with alkaline HPMCAS (Hydroxypropyl Methylcellulose Acetate Succinate) as the enteric coating layer, preferably having a pH in a range of from about 7 to about 10.

Substrate (Active Compressed Tablet Core)

<u>Ingredients</u>	<u>Quantity per tablet</u>
Omeprazole	20 mg
Lactose	192.5 mg
Magnesium carbonate	10 mg
Sodium starch glycolate	10 mg
Povidone	10 mg
Sodium stearyl fumarate	7.5 mg

Enteric coating layer

HPMCAS	16.1 mg
Triethyl citrate	4.5 mg
Sodium lauryl sulfate	0.5 mg
Talc	8.04
Sodium hydroxide	0.86 mg

5

For the preparation of the substrate, Omeprazole, together with lactose, magnesium carbonate, sodium starch glycolate, and povidone were mixed thoroughly. The mixture was then granulated with a sufficient quantity of water, and dried. Sodium stearyl fumarate was then added to the mixture, which was then compressed into tablets weighing 250 mg each.

10 These tablets, which formed the substrate of the composition, were then transferred into a conventional coating pan and coated with the enteric coating layer, prepared as described in Example 4.

Example 6

15 Stability tests were performed with formulations prepared according to Examples 2 and 3. For the first test, both coated and uncoated tablets prepared according to either Example 2 or Example 3 were placed into a box which was open to the environment. The open box was then stored at 40 °C and 75 % relative humidity, which are very stringent conditions. The coated and uncoated tablets were examined initially, after a week and after a month to determine stability.

20 The results are shown in the tables below.

10 In a second stability test, coated tablets were prepared according to Example 2. These coated tablets were then packed into an Alu/Alu (Aluminum/Aluminum) blister, which is a well known technique in the art for packing certain oral dosage forms. The blister was then stored under accelerated conditions of 30 °C and 60% relative humidity; or 40 °C and 75% relative humidity. Samples of the tablets were examined initially, and after one month of storage under one of these
15 conditions. In addition, samples were assayed to determine the amount of Omeprazole present in the coated tablet, as listed under “Assay” as milligrams of Omeprazole per tablet. A dissolution test was performed, using the accepted USP method. The coated tablets were placed in 0.1 N HCl for 2 hours, followed by a solution at pH 6.8 with stirring with a paddle at 100 rpm for 15 minutes, 30 minutes or 45 minutes. Gastric resistance was also examined by placing the coated tablets in a
20 simulated gastric fluid for 2 hours (pH of approximately 1), as is well known in the art. The results are shown in the table below.

	<u>Time (min)</u>	<u>Initial</u>	<u>30° 60 % RH</u>	<u>40° 75% RH</u>
Description	NA	Off white	Off white	Off white
Assay	NA	20.4 mg	19.39 mg	19.66 mg
Dissolution	120	0%	0%	0%
	135	52%	42%	39%
	150	96%	85%	90%
	165	105%	99%	104%
Gastric Resistance	NA	101%	98%	96%

These results show that the coated tablets, prepared according to Example 2, show good stability and gastric resistance, yet are also able to dissolve in an appropriate time-dependent manner.

5

Example 7

A one-way pharmacokinetic pilot study was performed *in vivo* for testing the pharmacokinetic profile of the coated tablets, which were prepared according to Example 2. The study was performed with ten healthy male volunteers, who received a single dosage of the coated tablets, containing 20 mg of Omeprazole. The results showed that Omeprazole administered in the coated tablets of the present invention had a similar lag time to absorption in comparison to a previous study performed with the reference product, which is the 20 mg Omeprazole dosage form of the formulation of Astra (Aktiebolaget Hassle), and also as described in the literature (see for example Duvauchelle, T. *et al.*, "Comparative Bioavailability Study of Two Oral Omeprazole Formulations After Single and Repeated Administrations in Healthy Volunteers", *Pharmacokinetics*, 16: 141-149, 1998). The lag time to absorption is defined as the time between the administration of the formulation and the first detection of the active ingredient in the samples taken from the subject, according to the sampling method employed.

In addition, comparable bioavailability was achieved with the coated tablets of the present invention, both to values obtained in the previous study with the reference product and to values which were described in the literature (see for example the previously referenced article in *Pharmacokinetics*). Furthermore, the values obtained for C_{max} and T_{max} concerning the rate of absorption were comparable to results obtained in the previous study performed with the reference product, and as described in the literature (see for example the previously referenced article in

20

Pharmacokinetics). Thus, the coated tablets of the present invention clearly show good performance both *in vitro*, as described in Example 6, and *in vivo*.

Example 8

Coated pellets were prepared according to the process previously described above in Example 4. However, the pellets were coated with the following suspension:

Enteric coating (quantities per capsule)

HPMCAS	21.00 mg
Triethyl Citrate	6.00 mg
Sodium lauryl sulfate	0.66 mg
Colloidal silicon dioxide	2.10 mg
Sodium hydroxide	1.12 mg

Example 9

Although the previous Examples used aqueous solutions for providing an optimal coating, the possibility of increasing the concentration of the enteric coating polymer by using an alcohol-based solution was studied in this Example.

Coated pellets were prepared according to the process of Example 4, except that these pellets were coated with the following solution, to obtain the required protection in an acidic environment.

Enteric coating

	Solution prepared	Quantities per capsule
Alcohol 95%	1.900 kg	N/A
Water	0.830 kg	N/A
HPMCAS	0.476 kg	21.00 mg
Triethyl citrate	0.136 kg	6.00 mg
Sodium lauryl sulfate	0.015 kg	0.66 mg
Colloidal silicon dioxide	0.047 kg	2.1 mg
Sodium hydroxide	0.025 kg	1.12 mg

Example 10

Substrate (Active Compressed Tablet Core)

<u>Ingredients</u>	<u>Quantity per tablet</u>
Omeprazole	20mg
Lactose	203mg
Magnesium carbonate	10mg
Sodium starch glycolate	10mg
Sodium stearyl fumarate	7mg

5 Enteric coating layer

<u>Ingredients</u>	<u>Quantity per tablet</u>
HPMCAS	16mg
Triethyl citrate	4.5mg
Sodium lauryl sulfate	0.5mg
Talc	8.14mg
Sodium hydroxide	0.86mg
Sepisperse™ (pink pigment)	10.8mg

For the preparation of the substrate, Omeprazole was mixed together thoroughly with lactose, sodium starch glycolate, magnesium carbonate and sodium stearyl fumarate. The mixture was then compressed into tablets weighing 250mg each. These tablets were then transferred into a conventional coating pan and coated with the enteric coating layer, prepared as described in Example 4, with the addition of a pigment to the enteric coating material.

Example 11

Stability tests were performed with the formulation prepared according to Example 10. For the tests, the tablets were packed into alu-alu blister. The blister was then stored under room temperature or under accelerated conditions of 30°C and 60% relative humidity (RH), or 40°C and 75% relative humidity. Samples of the tablets were examined initially and after 6 months of storage under one of these conditions. In addition samples were assayed. A dissolution test was performed, and gastric resistance was also examined. The tablet gave good stability results even

after storage at 40°C. The results are shown in the table below.

Test performed	Initial	25°C 6 month	30°C / 60%RH 6 month	40°C / 75%RH 6 month
Visual Description	conform	conform	conform	conform
Assay	19.76mg per tablet	20.19mg per tablet	19.97mg per tablet	19.28mg per tablet
Dissolution	96%	96%	96%	96%
Gastric Resistance	96%	96%	95%	94%

5 Example 12

A two-way pharmacokinetic study was performed in vivo for testing the bioequivalence of the coated tablets which were prepared according to Example 10, as compared to the reference product which is the 20mg Omeprazole dosage form of the formulation of Astra (Sweden), called Losec™. The study was performed on 39 volunteers. As shown in the table below, the results of the study showed that the two products exhibited very similar pharmacokinetic profiles, such that the two formulations can be considered to be bioequivalent.

Formulation	AUC (ng x hour/ml)	Cmax (ng/ml)	Tmax (hours)
Formulation of the present invention (Example 10)	426 ± 256	217 ± 109	1.08 ± 0.64
Losec™ (Astra)	434 ± 226	246 ± 113	1.56 ± 0.79

Example 13

Substrate (Active Compressed Tablet Core)

Ingredients	Quantity per tablet
Omeprazole	20mg
Lactose	203mg
Sodium hydrogen carbonate	10mg
Sodium starch glycolate	10mg
Sodium stearyl fumarate	7mg

5

Enteric coating layer

Ingredients	Quantity per tablet
HPMCAS	16mg
Triethyl citrate	4.5mg
Sodium lauryl sulfate	0.5mg
Talc	8.14mg
Sodium hydroxide	0.86mg
Sepisperse™	10.8mg

10 For the preparation of the substrate, Omeprazole was thoroughly mixed together with lactose, sodium starch glycolate, sodium hydrogen carbonate and sodium stearyl fumarate. The mixture was then compressed into tablets weighing 250mg each. These tablets were then transferred into a conventional coating pan and coated with the enteric coating layer, prepared as described in Example 4.

Example 14Substrate (Active Compressed Tablet Core)

<u>Ingredients</u>	<u>Quantity per tablet</u>
Omeprazole	20mg
Lactose	203mg
Trisodium citrate	10mg
Sodium starch glycolate	10mg
Sodium stearyl fumarate	7mg

5 Enteric coating layer

<u>Ingredients</u>	<u>Quantity per tablet</u>
HPMCAS	16mg
Triethyl citrate	4.5mg
Sodium lauryl sulfate	0.5mg
Talc	8.14mg
Sodium hydroxide	0.86mg
Sepisperse™	10.8mg

For the preparation of the substrate, Omeprazole was mixed thoroughly together with lactose, sodium starch glycolate, trisodium citrate and sodium stearyl fumarate. The mixture was then compressed into tablets weighing 250mg each. These tablets were then transferred into a conventional coating pan and coated with the enteric coating layer, prepared as described in Example 4.

Example 15

15 Stability tests were performed with the formulations prepared according to Examples 10, 13 and 14. Both coated and non-coated tablets were placed into an open box and stored at 40°C and 75% relative humidity, which are very stringent conditions. The coated and uncoated tablets were examined initially after 1 week and again after 2 weeks to determine stability. The results are shown in the tables below.

Tablets prepared according to Example 10

Sampled material	Appearance of sample		
	Initial	After 1 week	After 2 weeks
Coated	Pink	Pink	Pink
Uncoated	White	White	White

Tablets prepared according to Example 13

Sampled material	Appearance of sample		
	Initial	After 1 week	After 2 weeks
Coated	Pink	Pink	Pink
Uncoated	White	White	White

5

Tablets prepared according to Example 14

Sampled material	Appearance of sample		
	Initial	After 1 week	After 2 weeks
Coated	Pink	Pink	Pink
Uncoated	White	White	White

10

While the invention has been described with respect to a limited number of embodiments, it will be appreciated that many variations, modifications and other applications of the invention may be made.

WHAT IS CLAIMED IS:

1. A stable composition for a benzimidazole derivative, the composition comprising:
 - (a) a substrate, said substrate featuring the benzimidazole derivative; and
 - (b) an enteric coating material layered directly over said substrate, said enteric coating material having a pH value of at least about 6.5, thereby obviating the need for an intermediate layer between said substrate and said enteric coating, with the proviso that said enteric coating material does not include HPMCP (hydroxypropyl methylcellulose phthalate).
2. The composition of claim 1, wherein said substrate is an active core for containing the benzimidazole derivative.
3. The composition of claim 2, wherein said active core is selected from the group consisting of a pellet, a bead and a tablet.
4. The composition of claim 2, wherein said active core is a tablet formed by compression.
5. The composition of claim 1, wherein said substrate features:
 - (i) a neutral core; and
 - (ii) an active coating containing the benzimidazole derivative, said active coating being layered over said neutral core;such that the composition is in a form of a pellet
6. The composition of claim 1, wherein said substrate features a core containing the benzimidazole derivative with a suitable binding agent, said core being prepared by spheronisation and pelletization; such that the composition is in a form of a pellet.
7. The composition of claim 1, wherein said enteric coating material includes at least one enteric material selected from the group consisting of hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate,

hydroxypropyl methylcellulose phthalate, polymethacrylic acid methyl methacrylate and polymethacrylic acid ethyl methacrylate.

8. The composition of claim 7, wherein said enteric coating material further comprises an alkaline compound, such that said pH value is adjusted by adding said alkaline compound to said enteric material.

9. The composition of claim 8, wherein said alkaline compound is an inorganic alkaline compound.

10. The composition of claim 9, wherein said alkaline compound is selected from the group consisting of basic sodium, potassium and ammonium hydroxide.

11. The composition of claim 10, wherein said enteric coating material is at least about 60 % neutralized by adding said alkaline compound.

12. The composition of claim 11, wherein said enteric coating material is at least about 80 % neutralized by adding said alkaline compound.

13. The composition of claim 11, wherein said enteric coating material is at least about 95 % neutralized by adding said alkaline compound.

14. The composition of claim 8, wherein said pH value is in a range of from about 7 to about 10.

15. The composition of claim 8, wherein said enteric coating material further comprises a plasticizer.

16. The composition of claim 15, wherein said plasticizer is selected from the group consisting of a citric acid ester and a phthalic acid ester.

17. The composition of claim 1, wherein the benzimidazole derivative is selected from the group consisting of Omeprazole, Pantoprazole, Lansoprazole, Leminoprazole, Perprazole, Rabeprazole, and pharmaceutically acceptable salts thereof.

18. A stable composition for a benzimidazole derivative, the composition consisting essentially of:

- (a) a substrate, said substrate featuring the benzimidazole derivative; and
- (b) an enteric coating material layered over said substrate, said enteric coating material having a pH value of at least about 6.5 by an alkaline compound, such that said pH value is adjusted by adding said alkaline compound to said enteric material.

19. The composition of claim 18, wherein said substrate is an active core for containing the benzimidazole derivative.

20. The composition of claim 19, wherein said active core is selected from the group consisting of a pellet, a bead and a tablet, said active core being formed by embedding the benzimidazole derivative in poloxamer.

21. The composition of claim 19, wherein said active core is a tablet formed by compression.

22. The composition of claim 18, wherein said substrate features:

- (i) a neutral core; and
- (ii) an active coating containing the benzimidazole derivative, said active coating being layered over said neutral core.

23. The composition of claim 18, wherein said enteric coating material includes at least one enteric material selected from the group consisting of hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, polymethacrylic acid methyl methacrylate and polymethacrylic acid ethyl methacrylate.

24. The composition of claim 23, wherein said alkaline compound is an inorganic alkaline salt compound.

25. The composition of claim 24, wherein said alkaline compound is selected from the group consisting of basic sodium, potassium or ammonium hydroxide.

26. The composition of claim 25, wherein said enteric coating material is at least about 60 % neutralized by adding said alkaline compound.

27. The composition of claim 26, wherein said enteric coating material is at least about 80 % neutralized by adding said alkaline compound.

28. The composition of claim 27, wherein said enteric coating material is at least about 95 % neutralized by adding said alkaline compound.

29. The composition of claim 24, wherein said pH value is in a range of from about 7 to about 10.

30. The composition of claim 24, wherein said enteric coating material further comprises a plasticizer.

31. The composition of claim 30, wherein said plasticizer is selected from the group consisting of a citric acid ester and a phthalic acid ester.

32. The composition of claim 18, wherein the benzimidazole derivative is selected from the group consisting of Omeprazole, Pantoprazole, Lansoprazole, Leminoprazole, Perprazole, Rabeprazole, and pharmaceutically acceptable salts thereof.

33. A method for producing a stable composition for a benzimidazole derivative, the method comprising the steps of:

- (a) forming a substrate with the benzimidazole derivative;
- (b) preparing an enteric coating material having a pH value of at least about 6.5; and

- (c) layering said enteric coating material directly over said substrate, with the proviso that said enteric coating material does not include HPMCP (hydroxypropyl methylcellulose phthalate).

34. The method of claim 33, wherein said substrate is formed by melting poloxamer and by mixing the benzimidazole derivative into said poloxamer.

35. The method of claim 33, wherein said substrate is formed by direct compression.

36. The method of claim 33, wherein said substrate is formed by wet granulation.

37. The method of claim 33, wherein said substrate is formed by coating on an inert core.

38. The method of claim 33, wherein said enteric coating material is prepared by the steps of:

- (i) mixing an enteric material with water to form a mixture; and
- (ii) adding an alkaline compound to said mixture to form an aqueous solution having a pH value of from about 7 to about 10.

39. The method of claim 33, wherein said enteric coating material is prepared by the steps of:

- (i) mixing an enteric material with water and alcohol to form a mixture; and
- (ii) adding an alkaline compound to said mixture to form an aqueous solution having a pH value of from about 7 to about 10.

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(54) Title: STABLE BENZIMIDAZOLE FORMULATION

(57) Abstract: A stable composition with a benzimidazole derivative, such as Omeprazole, which does not contain a separating layer between the active compound and an enteric coating layer. Instead, the enteric coating layer is applied as a solution with a pH value of at least 6.5, and more preferably in a range of from about 7 to about 10, directly to the benzimidazole derivative substrate. This solution, with the optional addition of a plasticizer, can be directly coated onto the substrate without any necessity for an intermediate layer. Furthermore, in this pH range, the enteric coating is optionally applicable in an aqueous solution, thereby obviating the need for organic solvents for dissolving the enteric coating material. The resultant formulation maintains the stability of the benzimidazole derivative during storage and at the same time protects the product during passage through the acidic environment of the stomach. The problem of interaction between the enteric coat and the alkaline core is thus completely eliminated as the enteric coat at this stage is no longer acidic.

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Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled
STABLE BENZIMIDAZOLE FORMULATION

the specification of which

(check one)

☐ is attached hereto.

☒ was filed on DECEMBER 26, 2001 as United States Application No. or PCT International Application Number 10/018,992 and was amended on _____

(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Not Claimed

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